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Neurological Effects of Blast Injury

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Abstract

Over the last few years, thousands of soldiers and an even greater number of civilians have suffered traumatic injuries due to blast exposure, largely attributed to improvised explosive devices in terrorist and insurgent activities. The use of body armor is allowing soldiers to survive blasts that would otherwise be fatal due to systemic damage. Emerging evidence suggests that exposure to a blast can produce neurological consequences in the brain, but much remains unknown. To elucidate the current scientific basis for understanding blast-induced traumatic brain injury (bTBI), the NIH convened a workshop in April, 2008. A multidisciplinary group of neuroscientists, engineers, and clinicians were invited to share insights on bTBI, specifically pertaining to: physics of blast explosions, acute clinical observations and treatments, preclinical and computational models, and lessons from the international community on civilian exposures. This report provides an overview of the state of scientific knowledge of bTBI, drawing from the published literature, as well as presentations, discussions, and recommendations from the workshop. One of the major recommendations from the workshop was the need to characterize the effects of blast exposure on clinical neuropathology. Clearer understanding of the human neuropathology would enable validation of preclinical and computational models, which are attempting to simulate blast wave interactions with the central nervous system. Furthermore, the civilian experience with bTBI suggests that polytrauma models incorporating both brain and lung injuries may be more relevant to the study of civilian countermeasures than considering models with a neurological focus alone.

Keywords

Blast Injury; Traumatic Brain Injury; Polytrauma; Detonation

Introduction

Blast-induced traumatic brain injury (bTBI) is a major medical concern. During the Iraq conflict, nearly half of the soldiers who were injured experienced blast exposure resulting in neurotrauma[1] and bTBI has been called the “signature wound” of the Afghanistan and Iraq wars[2, 3]. While bTBI is a significant military health issue, it is also a civilian threat. Indeed, recent trends in global terrorism raise significant concerns for increases in civilian casualties caused by exposure to explosive devices[4]. Civilians typically do not wear protective equipment and are a more heterogeneous population that includes children and the elderly.

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As a result, the neurological consequences of exposure to a blast may differ between civilian and military populations. To explore the state of knowledge concerning bTBI, the National Institute of Neurological Disorders and Stroke (NINDS) convened a workshop in April, 2008. Co-sponsors included the Defense and Veterans Brain Injury Center, the Defense Center of Excellence for TBI and Psychological Health, the Department of Veterans Affairs, and the Interagency Committee on Disability Research. A multi-disciplinary group of neuroscientists, engineers, and clinicians shared insights on a number of topics including but not limited to: physics of blast explosions, acute clinical observations and treatments following exposure to blasts, in vitro, in vivo, and computational models, and lessons from the international community on civilian bTBI. Detailed information about the workshop, including the agenda, attendees, and supporting material, is available at the NINDS web-site [5]. The purpose of this paper is to provide an overview of the state of scientific knowledge in this important field by drawing from the published literature as well as presentations, discussions, and recommendations from the workshop.

Blast Injury Physics

Unlike collisions or impacts that typically are associated with trauma, explosive detonations produce transient shock waves that are characterized by a pressure transients that travel in excess of the speed of sound[6]. An idealized free-field spherical blast creates a temporal pressure transient, which can be modeled by the Friedlander function, that has a leading overpressure phase followed by a under pressure phase all occurring within milliseconds. However, explosives do not always combust instantaneously and multiple shock waves from one improvised explosive device (IED) can result. In addition, the blast wave is affected by reflection from nearby surfaces[7], potentially creating a merger of the initial pressure wave and reflected wave. Consequently, the idealized free-field description is rarely the clinical exposure scenario.

There are multiple types of injury caused by a blast event that are well documented in literature[1, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18]: 1) Primary blast injury caused by the direct effect of blast overpressure on organs, 2) Secondary blast injury resulting from shrapnel, objects, or materials hurled at victims, 3) Tertiary blast injury that occurs when victims are flung through the air and strike other objects, and 4) Quaternary blast injury characterized by burns produced by thermal effects from detonation. In addition, there are electromagnetic perturbations that occur with some types of explosions in particular those generated by IEDs that have metallic casings. These events result in the generation of small and brief radio-frequency pulses, for which the physiological impact is unclear and remains the subject of debate.

The current prevailing view is that the brain is a vulnerable target for blast injury, although the primary transduction pathway of blast energy to the brain is not well understood. For primary blast injury, there are at least three means by which transduction may occur: 1) through direct transcranial propagation; 2) via the vascular system; and 3) from the cerebrospinal fluid in the spinal cord to the foramen magnum. The role of the peripheral vasculature in the bTBI has been controversial. Dr. Ibolja Cernak (Johns Hopkins University Applied Physics Laboratory, Laurel, MD) based on many rodent studies has hypothesized that blast waves transfer kinetic energy through the vasculature and trigger pressure oscillations in blood vessels leading to the brain, whereas others have posited that the most likely transduction pathway is through direct transcranial propagation[19]. A study using a porcine model of blast overpressure, where systematic pressure measurements were made in various body structures, offered little support for the hypothesis involving pressure transmission through the vasculature[20]. However, consistent with Cernak's hypothesis, recent studies with rodents have shown that protection of the thorax and abdomen reduces

mortality due to blast and may also protect the brain[21]. These disparate observations suggest that there may be species differences in the role of peripheral vasculature in bTBI. With regard to human exposure, there have been several efforts to model the physics underlying the blast, incorporating skull and tissue properties to gain insight into how transduction may occur[10, 11]. While interesting and a potential complementary tool to discovery, the value of the computational modeling approach would be strengthened with validation studies. These validation studies could be accomplished through examination of human neuropathology or, more likely, the combination of computational, experimental animal work, and non-invasive clinical monitoring and neuroimaging.

Effects of Blast Exposure on the Brain and Neurological Function

Exposure to blast creates a spectrum of injury severities ranging from mild effects to fatal injuries. For injuries on the more severe end of the spectrum, most of our knowledge of the pathoanatomical consequences of bTBI is derived from studies of civilians. Edema, contusion, diffuse axonal injury (DAI), hematomas, and hemorrhage have all been observed following a bTBI[22, 23]. Reports from Iran and Afghanistan suggest that brain swelling occurs much sooner, within hours, after blast injury and mortality can be decreased by early decompressive craniectomy[12]. In an important study on military populations, Armonda and colleagues[24] reported that persistent traumatic focal cerebral vasospasm occurred in a substantial fraction of soldiers injured in a blast event. Moreover, the clinical outcomes of those patients exhibiting vasospasms were worse than those who did not. Following the study by Armonda et al.[24], vasospasm has also been recently described as a common and potentially underappreciated sequela of closed TBI[25]. Currently, most if not all of the neuropathological consequences of bTBI have also been observed following closed and/or penetrating TBIs. However, the neuropathological data on human blast injury are extremely limited and distinct differences may yet emerge.

Blast exposure on the milder end of the spectrum has also been reported to produce neurological complications loosely described as “shell shock” or “blast concussion.” The constellation of symptoms present after bTBI is varied, but like other types of TBI may include physical (somatic), behavioral, psychological, and cognitive symptoms. The symptoms are often referred to as post-concussive syndrome (PCS), and include retrograde amnesia, compromised executive function, headache, confusion, amnesia, difficulty concentrating, mood disturbance, alterations in sleep patterns, and anxiety[12]. As described by Lt. Col. David Benedek (Uniformed Services University of the Health Sciences, Bethesda, MD) at the Workshop, symptoms may be staggered in their onset, fluctuate in severity, and be triggered by life events months or possibly years after injury. The extent to which blast-induced pathoanatomical and biochemical changes in the brain account for these impairments is unclear. The severity of the blast exposure necessary to cause persistent symptoms is yet to be clearly identified. The effect of repeated mild blast exposures has also yet to be investigated, though recovery from post-concussive symptoms concussion is known to occur more slowly with successive head injuries.

Early evidence suggests that closed TBI and bTBI may produce very similar symptoms in terms of cognitive impairment[13]. In fact, Sayer and colleagues[26] reported no significant differences between blast and other injuries with regard to disturbances in pain, balance/equilibrium, motor functioning, vision, depression, or communicative abilities. Furthermore, the discernment of a reliable and distinct clinical profile for bTBI is further complicated by the frequent co-occurrence of bTBI with a closed and/or penetrating TBI[12]. As a result, causal factors for subsequent neurological impairment may be difficult to assign to one injury versus another. One distinct feature that may emerge for bTBI is an increased risk for hearing loss and tinnitus[27]. There may also be an increased incidence of post-traumatic

stress disorder (PTSD) symptoms[13, 26], but this is complicated because TBI and PTSD are often comorbid[14, 28, 29]. Both may be present and responsible for symptoms common to both conditions[12]. Misdiagnosis can occur in both directions, with bTBI mimicking PTSD and vice versa[30]. PTSD may be suspected in cases where psychological symptoms are the predominant complaints, whereas TBI or PCS may be associated with more cognitive, physical, and somatic symptoms[14]. An added challenge is that the symptoms of PCS may exist in the absence of a head injury[31]. This is also true for the co-occurrence of depression and TBI[32, 33].

Animal Behavior and Neuropathology Following Blast Exposure

Animal models of closed and penetrating types of TBI have been created to facilitate the development of diagnostic tools and medical interventions. Validation of the models requires comparison to human data in order to demonstrate that they reproduce one or more relevant features of the human injury. For both closed and penetrating TBI, seminal posttraumatic autopsy studies[34, 35] provided a foundation for validation of animal models. Less is known about the neuropathology associated with TBI of milder severity because most of these injuries are non-fatal.

Based on what is known about the neuropathology and neurological consequences of more severe clinical injuries, animal models have been developed for closed and penetrating TBI. Two of the most commonly used closed TBI models, the fluid percussion injury model and the controlled cortical impact model, both involve opening the skull and exposing the dura of the brain to a transient pressure wave[36, 37]. Although opening the skull would seem to be counterintuitive for producing a “closed” head injury, these models have been validated for reproducing relevant neuropathology and behavioral deficits associated with human TBI. Similarly, the inertial acceleration model of closed TBI produces DAI without any actual impact to the head. This too may seem counterintuitive since most clinical injuries involve a combination of impact and inertial forces. However, the utility of this model is its ability to reproduce and characterize the pathophysiology of a purely diffuse injury[38]. It is also important to note that the inertial acceleration model is only applicable for use with larger animals, such as swine. This is because the acceleration required to reproduce clinically relevant neuropathology is inversely proportional to brain mass, and thus exceeds the device’s capabilities for smaller animals, e.g. rodents. Additional differences in morphology, such as the brain surface, geometry, and white/gray matter ratios are also important considerations when designing clinically relevant models of TBI[39]. Thus, the animal models of closed TBI do not use devices to create known mechanical or physical parameters associated with human TBI, but rather to create whatever physical parameters or conditions are necessary to replicate the known clinical neuropathology.

Despite the caveats of developing animal models based on physical conditions or insult parameters associated with human injury, this has been a necessary approach for bTBI because of the limited knowledge of human neuropathology. Some of the more common models make use of blast tubes or structures that produce systematic and calibrated blast wave transients with peak pressure levels of approximately 20 to 350 kPa[7, 40, 41, 42, 43]. Open and contained field models have also been developed[7] to recreate more naturalistic blast environments. The field models are more complex and can potentially simulate all four types of blast injury (primary, secondary, tertiary, and quaternary). Alternatively, the blast tube models may be able to solely characterize the brain’s response to the primary injury, the direct response to the blast pressure wave. However, what is unknown is the extent which the brain experiences deformation in response to the primary blast. During the Workshop, Dr. Philip Bayly (Washington University, Saint Louis, MO) presented data on the use of dynamic, tagged magnetic resonance imaging (MRI), to enable real time

measurements of brain movement which may help address this question. His data demonstrated that even very mild linear and angular accelerations of the head create movement and shear strains in the brain.

Although it is virtually impossible to rigorously validate the bTBI models without more precise human data, these models appear to reproduce many of the overt neuropathological and behavioral deficits that have been described following human exposures (Table 1). For example, vasospasm, edema, contusion, axonal injury, and hemorrhage have all been described following blast injury in civilians or military populations[22, 23, 24] and have also been demonstrated in rodent and/or pig models[7, 20]. Transient alterations in electroencephalograms[44] and tympanic membrane perforations are associated with blast injury[45] and are also reproduced in some of the animal models[7, 46]. Cognitive deficits, a common and often major neurological consequence of human bTBI, have also been demonstrated with animal models[13, 23]. Human bTBI is often associated with other injuries, such as burns, limb amputations, hemorrhagic shock, etc., and in fact, there are very few clinical cases of individuals who have experienced only primary blast injury[47]. This observation has driven interest in the generation of an animal model of polytrauma to capture some of the added complexities of the injury[48]. However, PTSD and depression, which are strongly associated with human bTBI, have not been evaluated in the animal models. Seizures and posttraumatic epilepsy are well-known sequelae of all types of TBI, but especially penetrating injuries[49]. Reproducing post-traumatic seizures in an animal model of bTBI may require development of a polytrauma model that combines exposure to blast overpressure with a penetrating injury model[50].

The animal models have also provided some insights into the cellular and molecular pathophysiology of bTBI. Most, if not all of the pathophysiology described following experimental bTBI has also been observed in animal models of closed TBI[51, 52]. Neuronal, axonal and glial injuries have all been observed following bTBI[7, 41]. White matter seems to be more vulnerable in some studies[7]. Both apoptotic and necrotic pathways appear to contribute to neuronal death[51, 53]. The axonal injury may be attributable to the impairment of axonal transport and consequent accumulation of phosphorylated neurofilament proteins in neuronal cell bodies after blast exposure, similar to what has been observed in DAI[40]. Exposure to a nonlethal blast wave revealed widespread activation of microglia in the white and gray matter of the rat brain[54], consistent with activation of inflammatory processes. These neuroinflammatory responses have been observed within a day after exposure[54], and may be partially attributable to disruption of the blood brain barrier[55]. Oxidative damage is believed to mediate many of these processes[7, 51]. Inducible nitric oxide synthase (iNOS), an important modulator of cerebral blood flow, is elevated after blast exposure[41]. It has been suggested that iNOS may be a therapeutic target because administration of a specific inhibitor of iNOS attenuated the neurobehavioral deficits following bTBI in rats[42]. However, the beneficial versus detrimental effects of iNOS following TBI remain unclear and further experiments are warranted[56, 57]. Taken together, the pathophysiology of bTBI appears to be similar to that of closed TBI. Whether distinct differences and a signature profile will emerge for bTBI following comprehensive and systematic comparisons to closed and penetrating TBI, or whether the response to injury is truly similar remains to be determined.

Diagnostic Approaches for bTBI

Several groups are working toward the development of diagnostics technologies that can be used to detect brain injury after blast exposure. Xydakis and colleagues[45] demonstrated a significant correlation between tympanic membrane perforation and loss of consciousness in a multi-national cohort of people with blast exposures. However, recent work by Harrison et

al.[58] has called into question the value of tympanic membrane perforation for primary blast injury. During the workshop, Kestrel Corporation (Albuquerque, NM) presented results on the validity of oculomotor dysfunction as a neurobehavioral marker of TBI, suggesting that this could potentially serve as a field deployable diagnostic instrument. Banyan Biomarkers, Inc. (Alachua, FL) also reported during the workshop that biochemical markers related to alpha-spectrin degradation are under development for bTBI. Bauman et al.[7] reported that both neuron-specific enolase, a marker of neuronal damage, and myelin basic protein, a marker of injury to compact myelin, are elevated in serum of swine exposed to high magnitude blast overpressure of 340 kPa.

A potential biomarker for PTSD is also being investigated. Altered expression of p11 protein, a member of the large family of S100 proteins (S100A10), was observed following postmortem analysis of prefrontal cortex tissue in 46 known cases of PTSD[59]. Following this observation, Zhang and colleagues next demonstrated that real time PCR of peripheral blood mononuclear cells revealed significant decreases in p11 gene expression in PTSD patients compared with controls, suggesting potential diagnostic utility. However, whether p11 could serve as a biomarker for differential diagnosis of PTSD and TBI remains to be determined. At this time, little is known about the role of p11 after TBI. However, it is known that p11 is regulated by numerous factors, including growth factors, electroconvulsive therapy, and nerve lesions, and also interacts with a wide range of proteins[60]. Notably, evidence demonstrates that anti-depressants that target the serotonin receptor 1B (5-HT1B) require p11 interactions with the receptor to be effective[61]. Alterations in serotonin and depression, as well as other regulators and target proteins of p11 have also been observed following TBI[62]. However, further studies are needed to clarify the role of p11 and TBI.

Advances in neuroimaging are also poised to improve diagnostics following TBI[63]. In particular, diffusion tensor imaging (DTI) is of interest because of its potential to detect white matter damage, one of the most common problems after TBI, and one that is typically undetectable with conventional CT or MRI imaging. DTI is based on the understanding that water diffuses more rapidly in parallel with long fiber tracts as opposed to perpendicularly. By measuring diffusion in multiple directions, DTI enables voxel-wise calculations of fractional anisotrophy (FA), and thus the integrity of white matter tracts. Changes in FA following TBI have been correlated with functional recovery in a small study[64]. DTI can be used to generate maps of regional connectivity within the brain (tractography). A number of studies are ongoing to establish the role of DTI in detecting changes after bTBI[65, 66, 67].

Civilian Considerations in Blast Exposure

Terrorist attacks directed against civilian populations have emerged as a significant threat in the United States and abroad. Most terrorist attacks involve the use of explosive weapons producing a combination of blast, penetrating, and thermal injuries, and present a major challenge to civilian preparedness[4]. The absence of helmets and body armor in the civilian population worsens the mortality and morbidity of blast injuries. Similarly, the occurrence of a blast event in closed versus open settings impacts mortality and injury severity. In a retrospective study of blast incidents, there was a significant increase in injury severity and mortality rate in closed settings (buses) compared to open air, along with an increase in the percentage of primary blast injuries[17]. This may be attributable to a prolonged quasistatic overpressure, created by the reflection of the blast wave on the surfaces of the enclosed area (i.e. walls and floor)[7, 17, 18]. The intensity and duration of the observed overpressure during any singular event is dependent on the characteristics of the enclosed space[7, 17, 18]. The effect of closed vs. open settings was exemplified more recently during the Madrid bombing of four commuter trains in March 2004, where significantly increased fatality was noted in

the trains with closed versus open doors during the explosion[15]. Among those survivors requiring surgical attention, the percentage of people requiring general abdominal and neurosurgical interventions was 21% and 13%, respectively[15]. A retrospective analysis of all blast injuries admitted to the R. Adams Cowley Shock Trauma Center in Baltimore, MD, over a 10-year period showed that 36% of the victims were diagnosed with head injury where a subset had a negative admission CT with a subsequently positive CT for TBI over the next 48 hours[16]. Based on a summary of the Israeli experience at Hadassah-Hebrew University Medical Center over a 4 year span involving 93 mass-casualty terrorist attacks, the percentage of patients presenting with abdominal and head injuries was also high: 32% and 44%, respectively[68]. In addition, 52% of those injured in the terrorist bombings in the Israeli group suffered acute lung injury, necessitating lung protective ventilatory strategies during treatment[68]. As described by Dr. Yoram Weiss (Hadassah-Hebrew University Medical Center, Jerusalem, Israel) during the Workshop, a combination of head and chest injuries, which in their experience reached 20%, poses major challenges to medical management since best practice clinical guidelines for TBI and lung injury can be contradictory. Therefore, modifications to the guidelines may be necessary in order to maximize preservation of both brain and lung tissues. To this end, Weiss' group[68] has successfully used inhaled nitric oxide to overcome severe hypoxemia, which raised the oxygen saturation to at least 95% in brain injury patients, while also ameliorating the inflammatory effects in the lung. Overall, the civilian experience with bTBI suggests that polytrauma models of both brain and lung injuries may ultimately prove more useful in generating effective civilian countermeasures than considering a neurological focus alone.

Workshop Recommendations

The workshop presentations and discussions highlighted the need for a greater understanding of how blast exposure affects the human brain. The research into the pathophysiology of bTBI should include acute and long-term epidemiological studies, neurological assessment and imaging, and postmortem tissue analysis, when possible. A more complete characterization of the pathoanatomical and biochemical alterations that occur in the human brain following blast exposure will:

- Provide a foundation for the development and validation of computational, in vitro, and animals models of bTBI, including polytrauma models. Validated preclinical models will provide insights into the cellular and molecular mechanisms of bTBI, lead to the identification of therapeutic targets, and enable preclinical testing of drugs and other non-pharmacologic interventions.
- Enable systematic evaluation and comparison of the effects of bTBI to other physical causes of TBI, such as closed (impact and/or acceleration) and penetrating head injuries, and polytrauma. Further insight into the biological basis of acute and rehabilitation therapies for all types of TBI is essential, especially since the similarities and differences are incompletely understood. Standardization of terminology and data elements across studies is also encouraged to facilitate data sharing and systematic comparisons.
- Enable systematic evaluation and comparison of the effects of bTBI on military versus civilian populations. These two populations should also be considered in regard to prevention. Pre-treatment and protective gear may be practical for individuals with probable exposure to a blast event (i.e. military personnel), but not for civilians.
- Facilitate therapeutic development, including investigations into combination approaches. Given the complexity of TBI, plus the common occurrence of polytrauma, treatment for bTBI will most likely require the use of combined

therapies. Trials using combination therapies for traumatic brain injury are not common, although the research and development community is working to facilitate research in this area[69].

- Lead to Improvements in diagnosis for bTBI. Clinical pathoanatomical data is needed to validate imaging and other potential biomarkers. These studies are also necessary for translating the data collected in helmet and other sensors on the physical parameters of the blast to clinically meaningful effects on the brain. Complex multiscale modeling is needed to understand the effect of the blast event on neurological tissue and should be based on what is known about the pathophysiology, relating the forces that caused the injury with the biological result. In addition, diagnostic tools to discriminate between bTBI and PTSD are needed. Research aimed at developing more precise diagnoses for all types of TBI is a high priority across federal agencies[70].
- Provide a scientific underpinning for determining what effect, if any, the different components of a blast event have on the brain and how blast energy undergoes transduction to the nervous system. The field may need multiple models, species, and exposure forms to recreate the various components of the blast event and clinical manifestations.

Summary

It is now widely recognized that the brain is a vulnerable target for blast exposure. Along with this recognition comes the need to develop better diagnostic tools and more effective treatments for bTBI. To address this need, the Workshop was convened to discuss the state of the science, identify research gaps, and develop recommendations. A major observation was that to date, the preclinical and clinical data reveal few differences between bTBI and closed TBI. With regard to animal models, the physical features of the cranium and viscoelasticity of the heterogeneous tissue comprising the brain may be significant factors in developing an appropriate animal model and extracting relevant data. It may also be necessary to develop experimental paradigms that capture both the neurological and lung injury effects, modeling a “polytrauma blast syndrome.” While some may question the value of the computational modeling of human exposure to blast waves in the absence of validation, computational modeling may offer insight into potential differences that one might observe among animal models based on physical principles alone. There is progress being made in the identification of diagnostic markers of bTBI and PTSD; these encompass neurobehavioral testing, tympanic membrane perforation, quantitative measures of oculomotor function, advanced MRI imaging, and immunoassays based on serum or blood-based proteins. However, one of the most significant limitations is the lack of a well characterized, clinical neuropathology for bTBI.

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Table 1

Neuropathology and neurological consequences associated with bTBI by reference number.

	Human	Animal
Edema	22, 24	20
Vasospasm	24	7
Contusion	15, 22	21, 53
Axonal injury	22	7
Hematomas	15, 22	20
Hemorrhage	13, 23	20
Seizures	15, 23	
Tympanic membrane perforation	45	46
Polytrauma	4, 15	48
Cognitive deficits	13, 23	7, 41, 42
Post-Traumatic Stress Disorder (PTSD)	13, 30	
Depression	30	
Neuromotor deficits		7
Concussion or EEG alterations	12, 44	7